



BSRP-619

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:

U.S. Patent No. 4,916,246

:

ISSUED: April 10, 1990

:

TO: Ernst Felder, et al.

:

FOR: Paramagnetic Chelates Useful for
NMR Imaging

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FROM: Serial No. 002,115

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FILED: January 12, 1987

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Mail Stop Patent Ext.

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF THE TERM OF
U.S. PATENT NO. 4,916,246, UNDER 35 U.S.C. § 156

Sir:

Your applicant, BRACCO INTERNATIONAL B.V. ("BRACCO INT'L"), a corporation of the Country of The Netherlands and having a place of business at 3051 Strawinskylaan, 1077 ZX Amsterdam, The Netherlands, represents that it is the legal owner of Letters Patent of the United States No. 4,916,246, granted to Ernst Felder, Fluvio Uggeri, Luciano Fumagalli, and Giorgio Vittadini on the 10th day of April 1990 for Paramagnetic

2005E-0236

APP 1

Chelates Useful for NMR Imaging, by virtue of assignments recorded in the United States Patent and Trademark Office on the 12th day of January 1987 at Reel 4664, Frame 0166, on the 15th day of October 1993 at Reel 6728, Frame 0683 and at Reel 6728, Frame 0685, and on the 7th day of December 1993, at Reel 6790, Frame 0730; that both Bracco Diagnostics Inc. ("Bracco Diagnostics") and BRACCO INT'L are indirectly-owned subsidiaries of BRACCO S.p.A.; that BRACCO S.p.A. controls, indirectly, all the voting shares of Bracco Diagnostics and BRACCO INT'L; that Bracco Diagnostics is the owner of New Drug Applications ("NDAs") Nos. 21-357 and 21-358 for MULTIHANCE[®] (gadobenate dimeglumine), claimed by U.S. Patent No. 4,916,246; and that BRACCO INT'L is entitled to rely on the marketing approval for MULTIHANCE[®] (gadobenate dimeglumine) arising from NDAs Nos. 21-357 and 21-358.

Pursuant to the provisions of 37 C.F.R. § 1.730, your applicant hereby applies for an extension of the term of said United States patent of 5 years under 35 U.S.C. § 156, based on the materials set forth herein and in the accompanying papers. In the materials which follow herein, paragraph numbers correspond to the paragraph numbers in 37 C.F.R. § 1.740(a).

1. The approved product is MULTIHANCE[®], which is further identified as follows:

Chemical Name

Gadolate (2-), [4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)- N^5 , N^8 , N^{11} , O^4 , O^5 , O^8 , O^{11} , O^{13}]-, dihydrogen, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)

also known as

(4*RS*)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)]gadolate(2-) dihydrogen, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)

Generic Name

Gadobenate dimeglumine

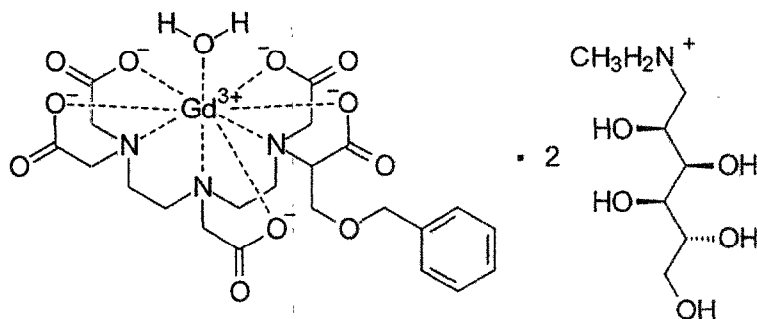
Molecular Formula

$C_{36}H_{62}GdN_5O_{21}$

Molecular Weight

1058.16

Chemical Formula (as hydrated)



2. MULTIHANCE[®] was subject to regulatory review under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355).

3. MULTIHANCE[®] received permission for commercial marketing or use under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) on November 23, 2004.

4. The active ingredient in MULTIHANCE[®] is Gadolinate (2-), [4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)-N⁵, N⁸, N¹¹, O⁴, O⁵, O⁸, O¹¹, O¹³]-, dihydrogen, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)(gadobenate dimeglumine). Said active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

5. This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. §§ 1.7 and 1.720(f). The last day on which this

application could be submitted is January 24, 2005, which is the next business day following the sixtieth day.

6. The patent for which an extension is being sought is identified as follows.

Inventors: Ernst Felder, Fluvio Uggeri, Luciano Fumagalli, and Giorgio Vittadini

Patent No.: 4,916,246

Title: Paramagnetic Chelates Useful for NMR Imaging

Issued: April 10, 1990

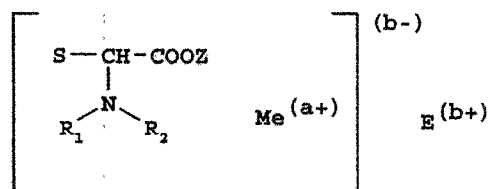
Expires: April 10, 2007

7. A copy of United States Patent No. 4,916,246, the patent for which an extension is being sought, is attached hereto as EXHIBIT A.

8. No disclaimer, certificate of correction or reexamination certificate has issued for United States Patent No. 4,916,246. A copy of the receipt of maintenance fee payment is attached hereto as EXHIBIT B.

9. United States Patent No. 4,916,246 claims the approved product. Claims 1-4, inclusive, claim the approved product *per se*. The manner in which each applicable patent claim reads on the approved product is as follows:

Claim 1 of U.S. 4,916,246 claims a genus of chemical compounds of the general formula



wherein:

a is 2 or 3;

b is an integer from 0 to 4;

Me^(a+) is Fe⁽²⁺⁾, Fe⁽³⁺⁾, Gd⁽³⁺⁾, or Mn⁽²⁺⁾;

E^(b+) is one or more physiologically biocompatible cation of an inorganic or an organic base or amino acid, said cation representing a total positive charge of b units;

S is the group -A-O-R wherein;

A is -(CH₂)_m-; -CH₂-C(CH₃)₂-;

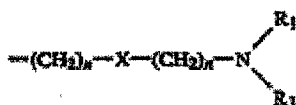
m is an integer from 1 to 5

R is H; linear or branched alkyl of 1 to 8 carbon atoms, said carbon atoms being unsubstituted or substituted by one or more hydroxy group [*sic*]; aralkyl of 1 to 4 aliphatic

carbon atoms; phenyl or phenyl substituted by halogen, amino or hydroxy; (poly)-oxa-alkyl of 1 to 10 oxygen atoms and from 3 to 30 carbon atoms;

R_1 is $-\text{CH}_2\text{COOZ}$; $-\text{CH}(\text{CH}_3)\text{COOZ}$; $-(\text{CH}_2)_n-\text{N}(\text{CH}_2\text{COOZ})_2$; hydroxy-arylalkyl radical, in which the aryl radical is unsubstituted or substituted by hydroxy;

R_2 is $-\text{CH}_2\text{COOZ}$; $-\text{CH}(\text{CH}_3)\text{COOZ}$;



wherein

R_3 is $-\text{CH}_2\text{COOZ}$; $-\text{CH}(\text{CH}_3)\text{COOZ}$; a monovalent radical having the structure S---CH---COOZ ;

X is a direct chemical bond; $-\text{O}-$; $-\text{S}-$; $-\text{NH}-$; $-\text{N---CH}_2\text{COOZ}$; $-\text{N---CH}(\text{CH}_3)\text{COOZ}$;

n is the integer 2 or 3, with the proviso that when X is a direct chemical bond, n is 1, 2 or 3;

Z is H or a negative charge.

When $\text{Me}^{(a+)}$ is $\text{Gd}^{(3+)}$, $(b-)$ is $(2-)$, $\text{E}^{(b+)}$ is dimeglumine, which is two physiologically biocompatible cations, having a total positive charge of $(2+)$, S is $-\text{A---O---R}$,

where A is linked to the rest of the molecule and is $-(CH_2)_m-$, where m is 1, R is aralkyl with 1 aliphatic carbon atom, which is also known as phenylmethyl or benzyl, R_1 is $-(CH_2)COOZ$, where Z is a negative charge, R_2 is $-(CH_2)_n-X-(CH_2)_n-NR_1R_3$, where n is 2, X is N- CH_2COOZ , and R_3 is $-(CH_2)COOZ$, where R_1 and Z are as defined before, then the compound is gadobenate dimeglumine. Gadobenate dimeglumine is represented in the chemical formula above, in the hydrated form.

Claim 2. The compound according to claim 1 wherein $Me^{(a+)}$ is $Gd^{(3+)}$.

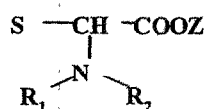
When $Me^{(a+)}$ is $Gd^{(3+)}$ and the remaining variables are as defined following claim 1 above, then the compound is gadobenate dimeglumine.

Claim 3. In a media for NMR contrast imaging which contains an agent for influencing relaxation time, the improvement which comprises said agent being a compound according to claim 1.

When the compound of claim 3 is as defined following claim 1 above, then the compound is gadobenate dimeglumine, which is a contrasting agent for influencing relaxation time in a media for NMR contrast imaging.

Claim 4. The compound of claim 1

wherein



is selected from the group consisting of

3-hydroxy-2-N-[2'-N'-[2''-N'',N''-bis-(carboxymethyl)-aminoethyl]-N'-(carboxymethyl)-aminoethyl]-N-(carboxymethyl)-amino-propionic acid,

3-phenylmethoxy-2-N-[2'-N'-[2''-N'',N''-bis-(carboxymethyl)-aminoethyl]-N'-(carboxymethyl)-aminoethyl]-N-(carboxymethyl)-aminopropionic acid,

3-methoxy-2-N,N-bis-[2'-N,N'-bis-(carboxymethyl)-aminoethyl]-aminopropionic acid,

3-phenylmethoxy-2-N,N-bis-[2'-N',N'-bis-(carboxymethyl)-aminoethyl]-aminopropionic acid,

4-(3,6,9,12,15-pentaoxahexadecyloxy)-3,3-dimethyl-2-N-[2'-N'-[2''-N'',N''-bis-(carboxymethyl)-aminoethyl]-N'-carboxymethyl)-aminoethyl-N-(carboxymethyl)-amino-butyric acid,

4-(3,6,9,12,15-pentaoxahexadecyloxy)-3,3-dimethyl-2-N, N-bis-[2'-N',N'-bis-(carboxymethyl)-aminoethyl]amino-butyrlic acid,

3-hydroxy-2-N-[2'-N',N'-bis-(carboxymethyl)-aminoethyl]-N-(carboxymethyl)-amino-propionic acid,

3-phenylmethoxy-2-N-[2'-N',N'-bis-(carboxymethyl)aminoethyl]-N-(carboxymethyl-amino-propionic acid,

3-octyloxy-2-N-[2'-N',N'-bis-(carboxymethyl)-aminoethyl]-N-(carboxymethyl)-amino-propionic acid,

N,N'-bis-(2-hydroxy-1-carboxy-1-ethyl)-N,N'-bis-(carboxymethyl)-ethylene diamine,

4-methoxy-3,3-dimethyl-2-N-[2'-N',N'-bis-(carboxymethyl)-aminoethyl]-N-(carboxymethyl)-amino-butyrlic acid,

3-phenylmethoxy-2-N-[2-[2'-N',N'-bis-(carboxymethyl)-aminoethoxy]-ethyl]-N-(carboxymethyl)-aminopropionic acid.

When the structure in claim 4 is the second listed structure, 3-phenylmethoxy-2-N-[2'-N'-[2''-N''N''-bis-(carboxymethyl)-aminoethyl]-N'-(carboxymethyl)-aminoethyl]-N-(carboxymethyl)-aminopropionic acid, and the remaining variables in the compound of claim 1 are as defined following claim 1 above, then the compound is gadobenate dimeglumine.

10. The relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows.

a. An exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act became effective for gadobenate dimeglumine on July 12, 1994, *i.e.*, the date a clinical hold was released for Investigational New Drug ("IND") Application No. 43,779.

b. New Drug Applications under section 505 of the Federal Food, Drug, and Cosmetic Act for MULTIHANCE® (gadobenate dimeglumine) were initially submitted on April 27, 2001 as NDAs Nos. 21-357 and 21-358.

c. NDAs Nos. 21-357 and 21-358 were approved on November 23, 2004.

11. A brief description of the significant activities undertaken by or for the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as EXHIBITS C and D.

12. Applicant is of the opinion that United States Patent No. 4,916,246 is eligible for an extension under 35 U.S.C. § 156, and the length of extension claimed is 5 years.

The requirements of 35 U.S.C. §§ 156(a) and (c)(4) have been satisfied as follows.

- a. U.S. Patent No. 4,916,246 claims a product, MULTIHANCE® (gadobenate dimeglumine).
- b. U.S. Patent No. 4,916,246 is currently set to expire on April 10, 2007 (*i.e.*, the term of the patent has not yet expired).
- c. The term of U.S. Patent No. 4,916,246 has never been extended.
- d. This application for extension is being submitted by BRACCO INT'L, the owner of record of U.S. Patent No. 4,916,246, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d).
- e. The product MULTIHANCE® (gadobenate dimeglumine), has been subject to a regulatory review period under section 505 of the Federal Food, Drug, and Cosmetic Act before its commercial marketing or use, and permission for said commercial marketing or use is the first permitted commercial marketing or use under the Federal Food, Drug, and Cosmetic Act.

- f. No patent as of this date been extended, nor has any other extension been applied for, on the basis of the regulatory review period which forms the basis for this application for extension of the term of U.S. Patent No. 4,916,246.

The length of extension of the term U.S. Patent No. 4,916,246 of 5 years claimed by applicant was determined according to the provisions of 37 C.F.R. § 1.775 as follows.

- a. According to 37 C.F.R. § 1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate according to paragraphs (d)(1) through (d)(6) of 37 C.F.R. § 1.775.
- b. Accordingly to 37 C.F.R. § 1.775(c), the regulatory review period is the sum of (A) the number of days in the period beginning on the date on which the exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act became effective and ending on the date the NDAs were initially submitted under section 505 and (B) the number of days in the period beginning on the date the NDAs were initially submitted and ending on the date the NDAs were approved. The exemption under subsection 505(i) became effective on July 12, 1994, the NDAs were

initially submitted on April 27, 2001 and the NDAs were approved on November 23, 2004. Accordingly, the regulatory review period is the sum of the periods from July 12, 1994 to April 27, 2001 and from April 27, 2001 to November 23, 2004. This is the sum of 2,481 days and 1,306 days, which is 3,787 days.

- c. According to 37 C.F.R. § 1.775(d)(1)(i), the number of days in the regulatory review period which were on or before the date on which the patent issued must be subtracted. Since U.S. Patent No. 4,916,246 issued on April 10, 1990 and the regulatory period began afterwards on July 12, 1994 (*i.e.*, the date on which the exemption under subsection 505(i) became effective), this section does not apply, and the regulatory period remains as 3,787 days.
- d. 37 C.F.R. § 1.775(d)(1)(ii) does not apply.
- e. According to 37 C.F.R. § 1.775(d)(1)(iii), the regulatory review period must then be reduced one-half of the days remaining in the period defined in 37 C.F.R. § 1.775(c)(1). This is one-half of 2,481 days, which is 1,240 days. After subtraction, and ignoring half days in the subtraction, this now leaves a reduced regulatory review period of 2,547 days.

- f. When the reduced regulatory review period of 2,547 days is added to the expiration date of U.S. Patent No. 4,916,246 (April 10, 2007), this gives a date of March 31, 2014. This latter date is earlier than November 23, 2018, the date obtained by adding 14 years to the date of approval of the approved product. Under paragraphs (d)(2) to (d)(4) of 37 C.F.R. § 1.775, applicant is entitled to an extension of patent term until a date that is no later than March 31, 2014, the earlier of the two dates of extension of patent term.
- g. The 5 year limitation of 35 U.S.C. § 156(g)(6)(A) and 37 C.F.R. § 1.775(d)(5) applies to this application, because U.S. Patent No. 4,916,246 issued after the date of enactment of 35 U.S.C. § 156. When 5 years is added to the expiration date of U.S. Patent No. 4,916,246 (April 10, 2007), this gives a date of April 10, 2012. This latter date is earlier than March 31, 2014, the date obtained by adding the number of days of the reduced regulatory review period to the expiration date of U.S. Patent No. 4,916,246. Therefore, under paragraphs (d)(2) to (d)(5) of 37 C.F.R. § 1.775, applicant is limited to an extension of 5 years to the term of the U.S. Patent No. 4,916,246. An extension of 5 years extends the expiration date to April 10, 2012. Accordingly, applicant is in

compliance with 35 U.S.C. § 156(g)(6)(A) and 37 C.F.R.

§ 1.775(d)(5).

13. Applicant acknowledges a duty to disclose the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the 5 year extension being sought to the term of U.S. Patent No. 4,916,246.

14. The prescribed fee for receiving and acting on this application for extension is to be charged to Deposit Account No. 18-1945, as authorized in the enclosed transmittal letter.

15. Please address all inquires and correspondence relating to this application for patent extension to:

Gregory J. Glover
ROPES & GRAY LLP
One International Place
Boston, MA 02110-2624
Tel.: 202-508-4600
Fax: 202-508-4650

16. A duplicate of these application papers, certified as such, is enclosed herewith.

17. A declaration as set forth in 37 C.F.R. §§ 1.740(a)(17) and 1.740(b) is enclosed herewith.

Respectfully submitted,

Date: January 21, 2005



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